Case-control studies for rare diseases: improved estimation of several risks and of feature dependences

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Abstract. *To capture the dependences of a disease on several risk factors, a challenge is to combine model-based estimation with evidence-based arguments. Standard case-control methods allow estimation of the dependences of a rare disease on several regressors via logistic regressions. For case-control studies, the sampling design leads to samples from two different populations and for the set of regressors in every logistic regression, these samples are then mixed and taken as given observations. But, it is the differences in independence structures of regressors for cases and for controls that can improve logistic regression estimates and guide us to the important feature dependences that are specific to the diseased. A case-control study on laryngeal cancer is used as illustration.*
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1 Introduction

1.1 Motivation and goals

Logistic regression models the dependence of a binary response variable on a set of regressor variables. These models have proven to be extremely successful tools in epidemiological and medical research, where the response is for instance survival or a disease diagnosis. In these models, the parameters measuring dependence are the log-odds ratios. And, in any two-way classifications of a response and a regressor, only functions of the odds-ratios remain unaffected by changes in the margins and hence by changes in the sampling schemes that allow to fix the overall count of the studied individuals, the row sums or the column sums; see Edwards (1963).

The variants of these models with exclusively categorical regressors are named logit regression; see Fienberg (1980, 2007). For logit regressions, goodness-of-fit tests compare how well the estimated counts agree with the observed counts. For general logistic regression instead, in which some of the regressors are quantitative and without replication for all level combinations, there is no similar formal test of goodness-of-fit. In such logistic regressions, a poor quality of the fitted values shows in increased standard deviations of the estimates but these give no direct pointers to locations of poor fit. Also, for some research questions, originally quantitative measures may not be of direct interest so that logit regressions can be focused on.

One may see it as an advantage of a model if it estimates in regions of sparse data by borrowing strength from portions of the data with many observations, however there is

the danger that conclusions are extrapolated to situations for which no data support is available, or to put it differently, for which evidence-based arguments are lacking since parameter estimates and statistical tests cannot be complemented by convincing basic data descriptions.

A special situation arises for case-control data. By design, such data are always samples from two different populations. There is one population of the cases, the individuals who have been diagnosed to have the disease under study and another population of the controls, the individuals without the disease.

For any rare disease, the cases constitute a tiny fraction of the general population in a given region at the time of study, so that for general public health decisions, the distribution of risk factors among the controls is of main interest. But for contemplating for instance a subsequent prospective study or the implementation of a small preventive screening program for those at highest risk, the main focus of interest are those combinations of risk factors and of other features that summarize best how the cases differ from the controls.

For case-control data, one conditions with each regression model on a mixture of data from two populations. The mixing proportions of one case to several controls are typically determined by cost considerations and, for rare diseases, they never define a sample of a real population. Dependences among regressors that exist either in the population of cases or in the population of controls may appear enlarged, diminished or get cancelled with the mixed sample values that are taken in regressions as the given observations of the regressors.

Therefore, we supplement the traditionally used logistic regressions for case-control data in two main ways. First, we obtain subgroups of cases and controls that are relevant for the main research questions and that are comparable in related, important features. Second, we carry out separate analyses for cases and for controls and exploit differences in dependence structures to obtain improved, smoothed estimates of odds-ratios and to identify important feature combinations that distinguish cases from controls.

1.2 Background information to laryngeal cancer and to regression graphs

Laryngeal cancer is currently the second most common cancer of the respiratory tract. Several risk factors have been reported in the literature. The risk in males increases with the amount and duration of tobacco consumption; see e.g. Zatonski et al. (1991), with regular alcohol consumption and with decreasing age at start of smoking, see e.g. Talamini et al. (2002). It decreases with an increasing time since ceasing to smoke; see IARC Monograph 83 (2003) and with only light inhalation when smoking cigarettes; see Ramroth et al. (2011). Differential susceptibility for laryngeal cancer in men and women may be related to hormones being involved in the carcinogenic process and to a gender-specific predisposition to develop laryngeal cancer; see Chen et al. (2011).

However, the understanding of the carcinogenic process and of the joint effects of alcohol and tobacco consumption is still limited. We focus mainly on the combination of these two well-established risk factors for laryngeal cancer when there are high exposures to both and when some of the intrinsic variables are comparable; see Berrington and Cox (2007) for a discussion of effects of intrinsic variables, which are characteristic of the study participants that cannot be modified by intervention, and see Cornfield et al. (1959), Cox and Wermuth (2003) for statistical aspects of causal relations.

Conditional independences identified separately in the sample of cases and in the sample of controls, lead to well-fitting, simplified dependence structures, to improved estimates of risks and to profiles of persons being at highest risk.

Regression graphs capture both independences and sets of directly important explanatory variables; see Cox and Wermuth (1993), Wermuth and Sadeghi (2012). Here, laryngeal cancer is the primary response of interest. Tobacco and alcohol consumption represent the two components of a joint response of secondary interest, which may depend on additional features of the participants that are considered to be also relevant for the occurrence of this type of cancer. The two components of the joint response are in turn joint risk factors for laryngeal cancer or, to put it differently, they are explanatory for the response of main interest.

Thus for a general population in which laryngeal cancer is rare, a first ordering of the variables in Figure 1 starts with the variable of main interest on the left, shows alcohol and tobacco consumption as intermediate between laryngeal cancer and several background variables, listed on the right, most of them being intrinsic features.

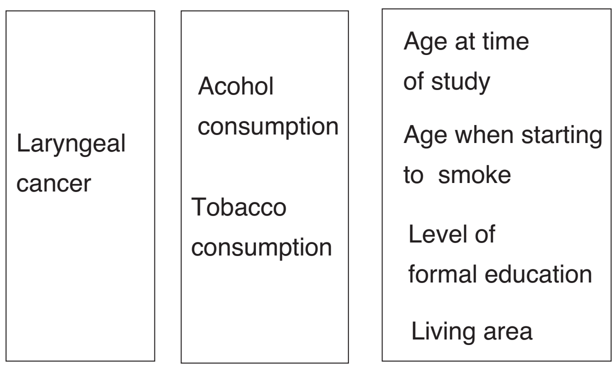

Figure 1: A first ordering of several variables relevant for laryngeal cancer.

A regression graph has nodes representing variables and an edge coupling a node pair for dependences that are important in generating the joint distribution. An arrow, $i \prec\!\!\!-\!\!\!-\, j$, points from a parent node j to its offspring node i, a dashed line, $i \,{-}{-}{-}\, j$, connects any two response nodes i, j if they are dependent given their joint set of parents and a full line, i —— j couples two background nodes i, j if they are dependent given all other background nodes.

For a regression graph constructed by statistical analysis from a case-control study, the arrows pointing to the disease result from estimated log odds-ratios and, for a general population of a rare disease, the dependence structure of all its potential regressors from an analysis of the controls alone. Additional insights can be gained by using more explicitly that, by the case-control sampling design, one has conditioned on each level of a binary response.

One consequence for all important regressors of the main response is that their dependence structures show, separately for the cases and for the controls, in graphs of only full lines, which have been named their induced concentration graphs; see Wermuth (2011). Different cliques for the same node subsets in these two types of graphs point to those dependence substructures of the features under study where the cases differ mainly from the controls, the disease diagnosis set again aside.

An induced concentration graph is Markov equivalent to a regression graph in the same node set and in the same set of edges if and only if it can be oriented such that no collision V results, that is no three-node, two-edge subgraph of either one of the types

$$i \succ\!\!\!\longrightarrow o \longleftarrow\!\!\!\prec j, \quad i\text{---}o \longleftarrow\!\!\!\prec j, \quad i\text{---}o\text{---}j\,;$$

see Wermuth and Sadeghi (2012). Thereby, the first ordering of the variables is taken into account, the order that captures the available knowledge about how the joint distribution is generated.

Some difficulty of variable ordering arises in case-control studies when age at the time of study does not have the same meaning for cases and controls. For the general population, studied with the sample of the controls, age is clearly the intrinsic variable of an individual. For the cases however, age is also a proxy for the length of exposure to risks and hence for a higher morbidity status and as such a consequence of exposure instead of a background variable.

1.3 Background information on the case-control study used as illustration

We use data from a Polish study of 249 males with exclusively glottic or subglottic tumors diagnosed in 1986 and 1987 in Lower Silesia; see Zatonski et al. (1991). The incidence rate of laryngeal cancer is reported for Lower Silesia as 35 in 100 000 for males aged 34 to 65 in the years 1984 to 1987; see Parkin et al. (1997).

Of the laryngeal cancer cases in this study, 80% were blue collar workers, 79% lived in an urban environment, that is in towns of more than 10 000 inhabitants, and 76% had less than 8 years of formal schooling. In this context, gender, age when cigarette smoking was started, living area are directly important intrinsic features while the level of formal schooling is also a crude indicator for the standard of living of blue collar workers in Poland at the time.

For this study, controls were selected from the electoral roll, with stratification by five-year age group and living area, rural versus urban. This stratification was used to ensure that the sampled proportions conform to those in the population, since the authors state that 'the age distribution among controls is closely representative of that of the general population within the age range 25 - 65 years, whereas the cases tend to be older.' Slightly fewer than 5 controls were recruited per case. Response rates in cases and controls were high at 88% and 94% respectively. This resulted in the participation of 249 cases and 965 controls, a total of 1214 men in the original study group.

1.4 Obtaining comparable relevant features of cases and controls

For a reliable estimation of the dependence of a disease on two or more specific risks, the choice of controls is critical. The studied groups of cases and controls need to be comparable with respect to other features that may distort these dependences when they are ignored. Such features have been called possible direct confounders; see Wermuth and Cox (2008).

In the literature on laryngeal cancer, tobacco consumption is typically described as a more important risk than alcohol consumption. We expect this to be different for high exposures and with the given data of the Polish study, we contrast high versus extreme exposures. The latter are long-term heavy vodka drinking and long-term heavy cigarette smoking.

The features considered as background variables, listed in the right-hand box of Figure 1, are possible direct confounders. In rural more than in urban Polish communities, heavy vodka drinking and heavy cigarette smoking may have been socially accepted. Cumulated exposure to these risks may increase with age at time of study and with the age when cigarette smoking was started. Poor nutrition leads to poor health and higher morbidity and may be more likely the lower the level of formal education.

To obtain comparable groups with respect to these possible confounders, we use the same constraints on the cases and controls of the original study group. Every selected man smoked on average 10 or more cigarettes per day, without any long non-smoking periods and without ceasing to smoke more than 4 years prior to the time of study. He started smoking 10 or more years before the time of study, at an age of 26 years or younger. Further, every selected man was at least 33 years old and had less than 12 years of formal schooling since, otherwise, there would have been not one comparable case in the rural communities.

The constraints taken together exclude more cases than controls, leaving 31% cases (48 of 156) in rural areas and 37% cases (156 of 424) in urban areas. Combined, there are 35% cases (204 of 580) in the selected study group compared to only 7% cases (45 of 634) in the subgroup excluded from the original study group.

We define seven binary variables from the given, available raw data. With $n = 580$ study participants and seven binary variables, the classification into $2^7 = 128$ level combinations gives 27% empty cells. Hence any estimation can be successfully combined with evidence-based arguments only if the data support many simplifying independences or if a dependence model has been shown to be appropriate in a previous, larger study.

The binary variables are L, laryngeal cancer (1:=case, 0:=control), V, heavy vodka drinking (1:=yes, regularly since 5 or more years, 0:=no), C, heavy cigarette smoking (1:=yes, more than 20 cigarettes per day, 0:=no, 10 to 20 cigarettes per day), A, older age group at time of study (1:=yes, 51 to 65 years, 0:=no, 33 to 50 years), E, lower level of formal education (1:=yes, less than 8 years, 0:=no, 8 to 11 years), S, starting age for cigarette smoking (1:=18 years or older but at least ten years before the time of study , 0:= 17 years or younger), R, region of living, (0:=rural, 1:=urban). Except for variables S and R, level 1 of the other four explanatory variables represents what is expected to be a higher level of risk for laryngeal cancer than level 0.

Tables 1 and 2 give the typical features for the four subgroups defined by the region of living, R, and the type of cigarette smoking, C.

Table 1: Features of the selected regular and heavy smokers in rural Polish communities

	regular smokers, $n = 103$				heavy smokers, $n = 53$			
feature	min	max	mean	std	min	max	mean	std
case, 0:=no, 1:=yes	0	1	22%		0	1	47%	
yrs of drinking hard liquor	0	30	2.3	6.62	0	30	7.4	10.74
$>$ 4 yrs heavy drinking, no/yes	0	1	12%		0	1	36%	
$<$ 8 yrs education no/yes	0	1	68%		0	1	74%	
age in yrs at time of study	33	64	48.8	10.22	33	64	49.6	8.83
age $>$ 50 yrs, no/yes	0	1	49%		0	1	49%	
age in yrs smoking started	10	26	18.1	2.58	12	26	18.2	3.09
start smoking $>$ 17 yrs, no/yes	0	1	67%		0	1	66%	
av. # cigarettes per day	10	20	17.2	3.16	21	60	30.0	8.29

By Tables 1 and 2, the four groups are comparable with respect to the intrinsic feature age when cigarette smoking was started. Within living areas, there are roughly similar percentages of participants with a low level of formal education. The average number of cigarettes smoked per day is comparable for rural and urban regular smokers (17.2 and 17.7) as well as for rural and urban heavy smokers (30.0 and 30.1).

With the four group sizes being quite different, the much higher average level of tobacco consumption for heavy smokers than for regular smokers requires conditioning on smoking, while the longer exposure to heavy vodka drinking in urban compared to

rural regular smokers requires conditioning on region when studying the effects of heavy vodka drinking in addition to heavy smoking.

The chances of seeing cases of laryngeal cancer range from 22% to 47% in the four groups. After merging the two groups of smoking given the regions or by merging the two regional groups given the levels of smoking, the proportion of cases would only vary between 31% and 37% for the two regions and between 31% and 47% for the two groups of cigarette smokers.

Table 2: Features of the selected regular and heavy smokers in urban Polish communities

	regular smokers, $n = 310$				heavy smokers, $n = 114$			
feature	min	max	mean	std	min	max	mean	std
case, 0:=no, 1:=yes	0	1	33%		0	1	46%	
yrs of drinking hard liquor	0	46	4.4	10.22	0	46	6.6	11.77
> 4 yrs heavy drinking, no/yes	0	1	17%		0	1	28%	
< 8 yrs education no/yes	0	1	57%		0	1	61%	
age in yrs at time of study	33	65	49.2	9.66	33	65	49.0	8.79
age > 50 yrs, no/yes	0	1	53%		0	1	46%	
age in yrs smoking started	7	26	18.5	2.71	9	26	18.0	2.80
start smoking > 17 yrs, no/yes	0	1	69%		0	1	65%	
av. # cigarettes per day	10	20	17.7	2.99	21	60	30.1	7.61

Thus by merging, one would give up the opportunity of investigating strong contrast in the numbers of cases to controls and marginal estimates could be distorted estimates of the conditional effects of heavy vodka drinking on laryngeal cancer.

2 Measures of marginal, conditional and overall dependence

2.1 Relevant recent results for different measures of dependence

For data obtained with a case-control design, the relation of counts for cases and controls depends on the number of selected controls per case and on the selection criteria. As one consequence, any observed percentage of cases does not translate directly into an estimate of the probability that the illness occurs.

When $n_{1\mathrm{y}}$ denotes the count of cases and $n_{0\mathrm{y}}$ the count of controls at high exposure to a risk factor (y:=yes), then the odds for cases versus controls are $n_{1\mathrm{y}}/n_{0\mathrm{y}}$, while otherwise they are $n_{1\mathrm{n}}/n_{0\mathrm{n}}$ for n:=no. For the study group of $n = 580$ men, the following table of counts and percentages gives as observed odds-ratio (odr) for laryngeal cancer, L, and heavy vodka consumption, V, as

$$\mathrm{odr}(LV) = (n_{1\mathrm{y}}n_{0\mathrm{n}})/(n_{0\mathrm{y}}n_{1\mathrm{n}}) = (349 \times 88)/(116 \times 27) = 9.8.$$

With a standard deviation of $\sqrt{1/349 + 1/88 + 1/116 + 1/27} = 0.245$ for $\log \text{odr}(LV)$, 9.8 represents a highly significant deviation from 1, the expected value of the odds-ratio when two binary variables are independent.

The observed odds-ratio for an illness and a risk factor, for instance $\text{odr}(LV)$, takes on a value of 1 if and only if the percentages of cases agree in the two categories of exposure. In addition, an odds-ratio approximates a relative risk for rare events. In this latter case, the odds expressed in terms of probabilities, say as $\pi/(1-\pi)$, are roughly the same as the probability for the rare event, π, itself. Thus, if a disease is rare in the population, odds ratios estimated in case-control studies, estimate relative risks in a population; see also Prentice and Pike (1979).

In Table 3, the observed odds-ratio $\text{odr}(LV) = 9.8$ differs substantially from the ratio of the observed percentages, 77/25= 3.1 and from the observed risk difference, $77 - 25 = 55$, the change in percentage points. However, the three measures always agree regarding a positive dependence of A on B given C, Z when A, B, C are binary variables and Z is vector background variable which may be a combination of categorical variables, of quantitative variables or consist of both types.

Table 3: Counts of laryngeal cancer cases for given levels of vodka consumption

	V, heavy vodka consumption		
L, laryngeal cancer	no	yes	sum
0:=controls	349	27	376
1:=cases	(25%) 116	(77%) 88	(35%) 204
sum	465	115	580
$\text{odr}(LV)$	9.8		

To be more precise, we denote a probability $\Pr(A = i, B = j, C = k, Z = z)$ by π_{ijkz}^{ABCZ} and marginal probabilities by summing over some of the levels +, so that for instance $\pi_{jkz}^{+BCZ} = \sum_i \pi_{ijkz}^{ABCZ}$ and the conditional probability of $A = 1$ given B, C, X is defined by $\pi_{1|jkz}^{A|BCX} = \pi_{1jkz}^{ABCZ} / \pi_{jkz}^{+BCZ}$.

If we denote further the odds for $A = 1$ given $B = 1$ and arbitrary levels of C, Z by $\mathcal{O}\text{d}(A|BCZ) = \pi_{11kz}^{ABCZ} / \pi_{01kz}^{ABCZ}$, and for $A = 1$ given $B = 0$ by $\mathcal{O}\text{d}(A|\bar{B}CZ)$, then the odds-ratios of AB given C, Z are $\mathcal{O}\text{dr}(AB|CZ) = \mathcal{O}\text{d}(A|BCZ)/\mathcal{O}\text{d}(A|\bar{B}CZ)$, the relative risks for $A = 1$ comparing $B = 1$ to $B = 0$ given C, Z are $\pi\text{rr}(A|BCZ) = \pi_{1|1kz}^{A|BCZ} / \pi_{1|0kz}^{A|BCZ}$ and the following three statements of positive conditional dependences

of A and B can be shown to equivalent; see also Theorem 1 of Xie, Ma and Geng (2008):

$$\begin{aligned} \pi\mathrm{rr}(A|BCZ) &> 1 && (1)\\ \mathcal{O}\mathrm{dr}(AB|CZ) &> 1 && (2)\\ \pi^{A|BCZ}_{1|1jz} - \pi^{A|BCZ}_{1|0jz} &> 0\,. && (3) \end{aligned}$$

The same types of relation hold for observed instead of expected contingency tables, as has been illustrated with Table 3. Equality in the three equations corresponds to conditional independence of A, B given C, Z, written compactly as $A \perp\!\!\!\perp B|CZ$.

If the conditional independence $A \perp\!\!\!\perp X|B$ holds, then the conditional density given B factorizes accordingly, as $f_{AX|B} = f_{A|B} f_{X|B}$ and any measure of dependence of A on B given X is unchanged after marginalising over X.

Given this result, one knows that two equal conditional odds-ratios for AB given a binary variable C coincide with the marginal odds-ratio, $\mathcal{O}\mathrm{dr}(AB)$, if $A \perp\!\!\!\perp C|B$. But, there is an additional sufficient condition, since the conditional odds, $\mathcal{O}\mathrm{d}(A|BC)$, relate via conditional probabilities to the marginal odds as

$$\mathcal{O}\mathrm{d}(A|BC) = \mathcal{O}\mathrm{d}(A|B)(\pi^{C|AB}_{1|11}/\pi^{C|AB}_{1|01})$$

Therefore, $\mathcal{O}\mathrm{dr}(AB|C) = \mathcal{O}\mathrm{dr}(AB)$ if the second term on the right-hand side does not depend on B, that is if $C \perp\!\!\!\perp B|A$. These two results together provide a direct proof of simple collapsibility of equal conditional odds-ratios for binary variables A, B over a binary variable C, that is

$$\{\mathcal{O}\mathrm{dr}(AB|C=0) = \mathcal{O}\mathrm{dr}(AB|C=1) = \mathcal{O}\mathrm{dr}(AB)\} \iff (A \perp\!\!\!\perp C|B \text{ or } B \perp\!\!\!\perp C|A)\,; \quad (4)$$

see also Whittemore (1978).

The same type of conditions as in (4) are sufficient but not necessary for simple collapsibility of equal odds-ratios when conditioning is on more variables or on categorical variable with more than two levels. In the framework of graphical models, these are discussed by Didelez, Kreiner and Keiding (2010) and Barenboim and Pearl (2011) as conditions for controlling selection bias for odds-ratios when there is outcome dependent sampling. However, conditions for simple collapsibility of equal relative risks given C are quite different from those for equal odds-ratios given C; see also Geng (1992).

If $B \perp\!\!\!\perp C$, then the marginal relative risk of A, B is an average of the conditional risks of A, B given both levels of C with positive weights adding to one:

$$\pi\mathrm{rr}(A|B) = \{\alpha\, \pi\mathrm{rr}(A|BC) + \beta\, \pi\mathrm{rr}(A|B\bar{C})\}/(\alpha + \beta)\,,$$

where $\alpha = \pi^{++C}_{1} \pi^{A|BC}_{1|01}$ and $\beta = \pi^{++C}_{0} \pi^{A|BC}_{1|00}$. Thus, positive conditional dependences always lead to a positive dependence after marginalizing over C and if the conditional

relative risks given C are equal, then they also coincide with the marginal relative risk for A given B that is

$$\{\pi\mathrm{rr}(A|BC) = \pi\mathrm{rr}(A|B\bar{C}) = \pi\mathrm{rr}(A|B)\} \iff (A \perp\!\!\!\perp C|B \text{ or } B \perp\!\!\!\perp C)\,. \tag{5}$$

There can be strong differences in conditional odds-ratios in spite of equal conditional relative risks and there can be strong differences in conditional relative risks in spite of equal conditional odds-ratios. Both results are useful for conclusions to be drawn from case-control studies, as shown here in Sections 3.5 and 4.

Possible effect reversal also needs attention. It is well-known that strongly dependent explanatory variables B, C can lead to a marginal positive dependence of A on B being reversed after conditioning on C, or vice versa, that conditionally positive dependences of A on B given C can be reversed when C is ignored. This is relevant only when variables B, C are two strongly dependent explanatory variables and there is, in addition, a qualitatively similar dependence of response A on B at the given levels of C. This can be deduced from the equivalent ways of expressing positive dependence in equations (1) to (3) in combination with Theorem 1 of Vellaisamy (2012).

In case-control studies, such situations may arise in logistic regressions with the disease as response, for instance, when two important regressors measure essentially the same risk, or when a strong dependence is induced between two important risk factors by the specific way in which samples of cases and controls are mixed in the given data.

2.2 The overall effects of the six observed, possibly explanatory variables

With Table 4, we report the overall odds-ratios for response L. It shows the variable pair in column 1, the observed overall odds-ratios for each variable pair in column 2 and the corresponding likelihood-ratio statistics for independence in column 3. Pearson's chi-square statistics for pairwise independence are displayed in column 4, Pearson's correlation coefficients for the binary variables in column 5 and Pearson's correlation coefficients as computed for the original binary and quantitative variables in column 6.

Table 4: Observed pairwise marginal dependences for $n = 580$

variable pair	odds-ratio	likelihood χ^2	Pearson's χ^2	Pearson's correlation binary	Pearson's correlation raw data
(L, V)	9.8	104.5	107.6	0.43	0.43
(L, C)	2.0	13.4	13.7	0.15	0.18
(L, A)	3.8	54.5	53.2	0.30	0.31
(L, E)	3.7	46.2	43.9	0.28	0.28
(L, S)	1.4	2.5	2.5	0.07	−0.01
(L, R)	1.3	1.8	1.8	0.06	0.06

Note that variable E has been coded to have 1:= lower level of education

The last two columns of the table show how little the correlation coefficients of the defined binary variables differ in size from correlations with the quantitative measurements in the raw data. In addition, the two types of chi-square statistics agree extremely well for the given set of data. In general, this is by no means the case since the likelihood ratio statistic is based on the odds-ratio and Pearson's chi-square statistic is instead a monotone function of the correlation coefficient of two binary variables.

A high agreement of the likelihood chi-square and of Pearson's chi-square can be expected when the binary data have two special properties: (1) none of the directly observed binary variables concerns a rare event and (2) the cutoff-points for the defined binary variables do not generate rare events. The latter happens, in particular, when the cutoff-point is near the median. This holds here since the observed percentages at level one are for L, V, C, A, E, S, R, respectively, in percent $35.2, 19.8, 28.8, 50.5, 61.2, 67.4, 73.1$.

The relevant, more general result is due to Cox (1966) who shows that the estimated slope in a simple logistic regression does not differ much from a linear regression coefficient whenever the observations at each of extreme levels of the response do not correspond to a rare event, that is to percentages smaller than 10%, say.

With r denoting a correlation coefficient of two binary variables and n the sample size, the value of Pearson's chi-square statistic is nr^2; for a proof see for instance Wermuth and Streit (2007), p. 344. Expressed differently, for $n = 580$, an absolute value of these observed correlation coefficients larger than $0.11 = \sqrt{6.63/580}$ is statistically significant at a 0.01 level, of 0.14 at a 0.001 level.

3 The dependences for laryngeal cancer on several factors

3.1 Logit regressions for $\boldsymbol{L}$ as response to $\boldsymbol{V, C, R}$

The observed dependences of laryngeal cancer, L, on heavy vodka drinking, V, are shown first for the two regions and given regular versus heavy cigarette smoking.

Table 5: Counts, percentages and observed odd-ratios for L, V given C in rural regions

L, laryngeal	levels of V, C (heavy drinking/ heavy smoking)			
cancer	no/no	yes/no	no/yes	yes/yes
controls	73	7	26	2
cases	(20%) 18	(42%) 5	(24%) 8	(89%) 17
sum	91	12	34	19
odr$(LV\|C, R = 0)$	2.9		27.6	

Table 5 is for rural communities. It shows a much stronger dependence of laryngeal cancer on heavy vodka drinking when the men are heavy cigarette smokers than when

they are regular but not so heavy smokers. By contrast for urban communities, Table 6 shows a much stronger dependence of laryngeal cancer on heavy vodka drinking when the men are regular cigarette smokers than when they are heavy smokers.

Table 6: Counts, percentages and observed odd-ratios for L, V given C in urban regions

L, laryngeal	levels of V, C (heavy drinking/ heavy smoking)			
cancer	no/no	yes/no	no/yes	yes/yes
controls	198	9	52	9
cases	(23%) 60	(83%) 43	(37%) 30	(72%) 23
sum	258	52	82	32
odr$(LV\|C, R = 1)$	15.8		4.4	

The corresponding logit model is written as $L:\ V * C * R$ in Wilkinson's notation for generalized linear models; see e.g. McCullagh and Nelder (1989). It includes with an important 3-factor interaction effect of V, C, R on L also all main effects and all 2-factor effects so that the parameters are those of the saturated, i.e. the unconstrained, logit regression and the maximum-likelihood estimates of the expected counts agree with the observed counts.

The 3-factor interaction in the logit regression is estimated in terms of the four observed odds-ratios in Tables 5 and 6 as

$$\log(4.43/15.77) - \log(27.62/2.90) = -3.52$$

with an estimated standard deviation of 1.22, giving $z_{\text{obs}} = -3.52/1.22 = -2.9$.

We denote any estimated highest-order logit term divided by its standard deviation by z_{obs}, as it can roughly be viewed as a realisation of a Gaussian random variable that is standardized to have zero mean and unit variance, provided the population term is zero. With a p-value of 0.002, the 3-factor interaction is highly significant so that the dependence structure in Tables 5 and 6 cannot be simplified.

Alternatively, the same judgement is reached with a likelihood-ratio goodness-of-fit test for $L:\ (V + C + R)^2$, the logit model with just the 3-factor interaction term of V, C, R on L removed from the saturated model. With a chi-square value of 9.2 on 1 degree of freedom (df) and $\sqrt{9.2} = 3.0$, again roughly the value of a standardized Gaussian distribution if the model fits, the agreement with the absolute value of the above reported $z_{\text{obs}} = -2.9$ is high, as expected.

3.2 Dependence of $\boldsymbol{L}$ on $\boldsymbol{V, C, R}$ based on structure for cases and controls

For controls and for cases, the observed VCR table of counts are contained within the tables of counts shown in Tables 5 and 6. For controls, these counts are well compatible

with $VC \perp\!\!\!\perp R$ so that the rates of heavy versus regular cigarette smokers are estimated by the overall observed percentages of heavy vodka drinking given C, for regular smokers with 5.6% versus 12.4% for heavy smokers. Thus, the risk for heavy vodka drinking at the level of 5.6% is more than doubled when one looks at the control group of heavy cigarette smokers compared to the control group of regular smokers.

For cases, there is a different, more complex dependence structure for V, C, R. For cases in rural communities, vodka drinking is strongly increased when they are also heavy cigarette smokers; from 22% to 68%. Thus the risk of heavy vodka drinking starts at a level that is considerably higher than for any of the control groups and the relative risk of heavy vodka drinking is estimated to be at a factor of about 3 for heavy compared to regular smokers; with 68/22=3.1. For cases in urban communities instead, heavy vodka drinking is observed at essentially the same rates for regular and heavy cigarette smokers with 42% and 43%; see Table 7.

Table 7: Heavy vodka drinking for cases by cigarette smoking and living area

V, heavy	R rural, C heavy smokers		R urban, C heavy smokers	
vodka drinking	no	yes	*no*	yes
0:= no	18	8	60	30
1:=yes	(22%) 5	(68%) 17	(42%) 43	(43%) 23
odr($VC|R$)	7.7		1.1	

These basic data summaries in terms of the observed counts point to the differences in exposure that explain already to a large extent the observed interactive effect of V, C, R on L. They supplement the maximum-likelihood estimates of the probabilities at the two levels of L which can be expressed formally for $L = 0$ and $L = 1$ as

$$\hat{\pi}^{LVCR}_{0jkl} = n_{0jk+}n_{0++l}/n^2_{0+++} \text{ and } \hat{\pi}^{LVCR}_{1jkl} = n_{1jkl}/n_{1+++}\,,$$

when n_{ijkl} denotes the observed count in the $LVCR$ table and summing is indicated by the +-notation in the same way as for probabilities. These are the estimates for two graphical log-linear models; see Darroch, Lauritzen and Speed (1980). Their graphs are also known as concentration graphs. The model for the controls has tables VC and R as the set of minimal sufficient statistics and the model for the cases needs table VCR to generate the joint distribution.

These types of models have representations in terms of undirected graphs with nodes for variables but at most one full-line edge coupling each node pair. For exclusively categorical variables, the set of minimal sufficient statistics of the model coincides with the set of cliques in the graph. For a clique, each node is coupled to all other nodes within the clique, and an incomplete graph is induced when just one further node of the

graph is added to the nodes of a clique. In case-control studies these models arise as independence structures that one can study directly for cases and for controls separately.

No graph distinguishes between additive and interactive effects, but each graph permits to read off the graph all independence statements that the model implies; the criterion for full-line graphs is given in connection with Figure 3 below. The two graphs relevant here for VCR given L are the two simple graphs in Figure 2.

For the cases, there is a complete graph so that no independences are implied. For the controls, nodes VC are coupled by an edge and are isolated from node R. This captures $VC \perp\!\!\!\perp R$ as well as independences that follow from the model, for instance, $V \perp\!\!\!\perp R|C$ or $V \perp\!\!\!\perp R$.

Figure 2: Graphs capturing the independence structure of V, C, R a) for controls, b) for cases.

By combining the counts estimated separately for controls and cases, shown in Table 8, smoothed odds-ratios result compared to a logistic regression which uses implicitly the structure of two complete concentration graphs. The graphs summarize the estimated independence structure in the populations of either the cases or of the controls, for a set of variables that is directly explanatory for the disease.

Table 8: Estimates, obtained with separate models of VCR for cases and controls

L, laryngeal	levels of V, heavy vodka drinking; C, heavy smoking; R, rural							
cancer	000	100	010	110	001	101	011	111
controls	77.8	4.6	22.4	3.2	193.2	11.4	55.6	7.8
cases	18	5	8	17	60	43	30	23
$\hat{\mathcal{O}}\mathrm{dr}(LV\|CR)$	4.7		15.1		12.1		5.4	

Smoothed, estimated odds-ratios obtained from counts in several cliques of graphs are based on observations for more individuals than those using complete graphs. This leads to smaller standard deviations of the estimated odds-ratios and hence to more reliable results; provided only that the structures in the populations are well estimated.

The larger the numbers of observation, the more likely it is that this goal is reached, unless there are variables that show extremely strong dependences. Even if results appear to be reliable in this sense, confounding effects of additional variables need to be

ruled out, here those of A, E, S. In the next sections, we do this first by using logistic regressions with enlarged sets of regressors, next by exploiting again independences.

3.3 Effects of $\boldsymbol{A}$, $\boldsymbol{E}$ or $\boldsymbol{S}$ on $\boldsymbol{L}$ in logit regressions when added to $\boldsymbol{V, C, R}$

To contemplate directions of effects of A, of level of formal schooling, E, and of age when starting to smoke, C, is to follow R.A. Fisher's advice of making 'theories elaborate' as quoted by Cochran (1965), that is 'when constructing a causal hypothesis one should envisage as many different consequences of its truth as possible'.

Since age at the time of study, A, is for cases partly a proxy for cumulated exposure to several risk factors, currently known or still unknown, one can also expect that the illness occurs more frequently the higher the age at study time, so that there is an increasing, additive effect of A on L. The level of formal schooling, E, could have a similar effect since it correlates strongly with A. On the other hand, since there is no overall effect of S, age when cigarette smoking was started, one expects no direct effect of S, when V, C, R, A or V, C, R, E are already used to predict L.

In the logit models for L that include in addition either age at study time, A, or level of education, E, the three-factor effect term for VCR remains significant and there is an additional significant main effect of the added variable. The goodness-of-fit of each of the models can then be tested and is very good for model $L : V * C * R + A$ with a chi-square value of 4.1 on 7 df, it is a bit less convincing, looked at alone, for model $L : V * C * R + E$, where there is a chi-square-value value of 10.1 on 7 df.

Since the observed tables of counts for $LVCRA$ and $LVCRE$ are too sparse to report sensible percentages, Table 9 shows only the observed odds-ratios. They confirm that the general pattern of the dependences in Tables 5, 6 is approximately repeated given the two levels of either A or of E, so that an additive main effect, in addition to the interactive effect of VCR is a plausible description of the observed odds-ratios. Indeed, they are close to the odds-ratios estimated under the two models $L : V * C * R + A$ or $L : V * C * R + E$, shown in Table 10.

Table 9: Observed odds-ratios for laryngeal cancer, L, and heavy vodka drinking, V

	level combinations of CRA or CRE							
	000	100	010	110	001	101	011	111
odr($LV\|CRA$)	1.4	34.0	11.2	3.5	5.3	19.8	20.3	4.2
odr($LV\|CRE$)	-	27.0	18.5	15.5	8.0	34.0	12.3	2.6

In Table 10, the estimates at level 0 of A are repeated at level 1 of A. At all levels of CRA or CRE, a strong dependence of laryngeal cancer on heavy vodka drinking is estimated, for instance with an odds-ratio of $\hat{\mathcal{O}}\mathrm{dr}(LV|C = 0, R = 0, A = 0) = 3.1$, for

rural regular smokers in the younger age group and with $\hat{\mathcal{O}}\text{dr}(LV|C = 1, R = 0, A = 0) = 27.3$ for rural heavy smokers in the older age group.

Table 10: Estimated odds-ratios for L and V for models $L : VCRA$ and $L : VCRE$

	level combinations of CRA or CRE							
	000	100	010	110	001	101	011	111
$\hat{\mathcal{O}}\text{dr}(LV\|CRA)$	3.1	27.3	14.4	3.8	3.1	27.3	14.4	3.8
$\hat{\mathcal{O}}\text{dr}(LV\|CRE)$	3.6	30.9	14.3	4.5	3.6	30.9	14.3	4.5

Instead variable S, age when cigarette smoking had been started, does not improve prediction of L if added to V, C, R, A since none of the one df components is large for 15.4 on 16 df, the chi-square value resulting when model $L \perp\!\!\!\perp S|VCRA$ is fitted. Overall, these added logit regressions appear to support the hypotheses about the effect directions. However, more insight is gained by exploiting again independences present for cases or for controls.

3.4 The independence models $A \perp\!\!\!\perp VR|CL$ and $V \perp\!\!\!\perp R|ACL$

For $VACR$ given L, we compare first two independence models that are graphical log-linear models, $A \perp\!\!\!\perp VR|CL$ and $A \perp\!\!\!\perp V \perp\!\!\!\perp R|L$, with the logit regression model $L : A + V * C * R$. Several special features show by conditioning explicitly on cases and controls.

The graph of model $A \perp\!\!\!\perp VR|CL$ is given in Figure 3. For every statement $a \perp\!\!\!\perp b|c$ implied by this model for disjoint subsets a, b, c of $\{A, V, R, C, L\}$, every path from a to b has a node in c. Thus in particular, every path from A to $\{V, R\}$ passes through C or L and, for instance with strong dependences of L on each of V, A, a dependence between V and A, which is absent given L, C, R, will be introduced by marginalising over L.

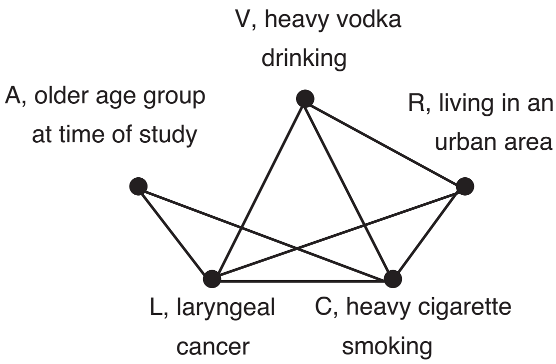

Figure 3: Concentration graph of model $A \perp\!\!\!\perp VR|CL$; likelihood chi-square: 4.7 on 12 df.

Table 11 shows how little the observed counts deviate from estimates under model $A \perp\!\!\!\perp VR|CL$ that is for heavy vodka drinking, V, and urban living area, R, conditionally

independent of the age groups at study time, A, given C and cases or controls. It also contains the fitted counts for model $A \perp\!\!\!\perp V \perp\!\!\!\perp R|L$ and the $VARC$ table.

Table 11: Observed counts for the $VARCL$ table and estimates for $A \perp\!\!\!\perp VR|CL$

				controls			cases			combined	
$VACR$ levels				count	estim.*	perc.*	count	estim.*	perc.*	count	percent
0	0	0	0	41	43.24		6	4.14		47	
1	0	0	0	5	4.15	8.7	1	1.15	21.7	6	11.3
0	1	0	0	32	29.76		12	13.86		44	
1	1	0	0	2	2.85	8.7	4	3.85	21.7	6	12.0
0	0	1	0	17	16.94		3	3.08		20	
1	0	1	0	1	1.30	7.1	6	6.54	68.0	7	25.9
0	1	1	0	9	9.06		5	4.92		14	
1	1	1	0	1	0.70	7.1	11	10.46	68.0	12	46.2
0	0	0	1	118	117.28		14	13.81		132	
1	0	0	1	6	5.33	4.3	8	9.90	41.7	14	9.6
0	1	0	1	80	80.72		46	46.19		126	
1	1	0	1	3	3.67	4.3	35	33.10	41.7	38	23.2
0	0	1	1	35	33.89		14	11.54		49	
1	0	1	1	5	5.87	14.8	7	8.85	43.4	12	19.7
0	1	1	1	17	18.11		16	18.46		33	
1	1	1	1	4	3.13	14.8	16	14.15	43.4	20	37.7

*estimated counts for model $A \perp\!\!\!\perp VR|CL$ with deviance 4.7 on 12 df; percent for estim. $V = 1$

By mixing the samples from the two different populations, the cases and the controls, for the $VARC$ table, a sizeable dependence of V on A given RC results. This shows in the percentages in the last column of Table 11, which vary widely within some of the fixed levels of C, R. If we had data from a prospective study with L as response occurring in the future of the explanatory variables, it would be impossible to induce any dependence by marginalizing over L.

For interpretation, the important feature of model $A \perp\!\!\!\perp VR|CL$ is that it implies $V \perp\!\!\!\perp A|CRL$. Therefore, for heavy vodka drinking, V, marginalizing over A leaves the dependence of V on C unchanged for all level combinations of R, L. This explains why the estimated rates of heavy vodka drinking given this model coincide with those observed for the VCR tables at both levels of L. In particular, the estimated rates for cases in Table 11, repeat for the two levels of A and are identical except for rounding errors to the rates for cases in the observed VRC table of Table 7.

For model $V \perp\!\!\!\perp R|CVL$, the fit seems to be good with no large component chi-square value in the eight tests for independence of pair V, R defined by the combinations of

C, V, L; the sum giving a chi-square value of 11.0 on 8 df and a p-value of 0.20. Its graph arises from the one in Figure 3, by adding the two edges A —— V, A —— R and removing V —— R. However, the fitted odds-ratios for L, V differ substantially from the observed values in Table 9, while those of the other two models in Table 12 agree well.

Table 12: Odds-ratio estimates for L, V given CRA under selected models

		level combinations of CRA							
	$\hat{O}\mathrm{dr}(LV\|CRA)$ for:	000	100	010	110	001	101	011	111
logit	$L: A + V * C * R$	3.1	27.3	14.4	3.8	3.1	27.3	14.4	3.8
log-linear	$A \perp\!\!\!\perp VR\|CL$	2.9	27.6	15.8	4.4	2.9	27.6	15.8	4.4
	$V \perp\!\!\!\perp R\|ACL$	6.5	6.6	6.5	6.6	15.1	6.7	15.1	6.7

This can be explained. The sparser a table gets, the more difficult it becomes to decide among seemingly well-fitting models. If here the independence of pair V, R is considered in addition to the extremely well-fitting model $A \perp\!\!\!\perp V|RCL$ having a p-value of 0.97, then it becomes a test in the marginal table $VCRL$ and leads to a poorly fitting model with a p-value of only 0.03; derived from a chi-square value of 10.7 on 4 df.

3.5 Further mixed count estimates to obtain smoothed odds-ratios

Though there is with $A \perp\!\!\!\perp VR|CL$ a well-fitting independence structure for both cases and controls, we expect substantial differences of the dependences and independences in the two populations. After all, the main purpose of a case-control study is to gain an understanding of what the differing features and dependences are of those who have been diagnosed to have the disease from those who have not.

For cases and controls analyzed separately, two well-fitting structures are captured by the graphs in Figure 4. They may for instance be derived by forward selection in the general class of concentration graphs with a goodness-of-fit criterion for the selected edges of $p = 0.2$; see Højsgaard, Edwards and Lauritzen (2012).

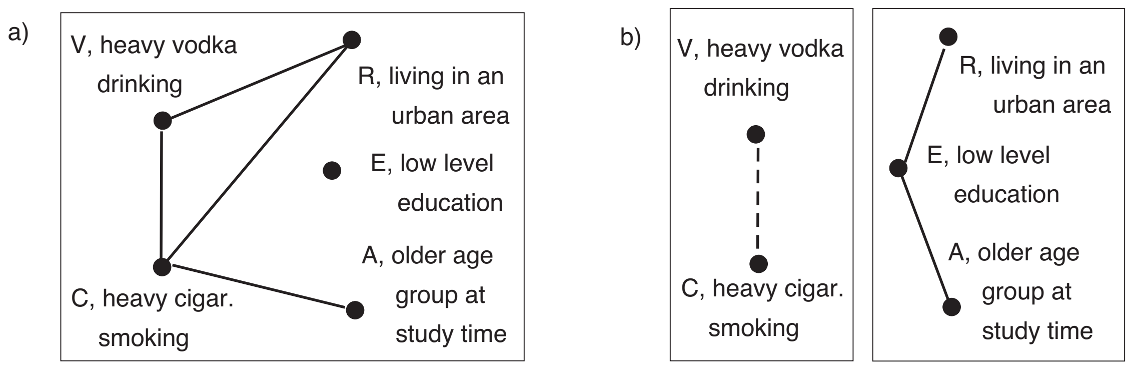

Figure 4: Graphs of two separate well-fitting models for V, C, R, A, E a) a concentration graph for cases with a fit of 16.2 on 21 df; b) a regression graph for controls with 17.9 on 23 df.

The count estimates are reported in Table 19 in the Appendix and the estimates of the conditional odds-ratios based on the separate models for cases and controls to the graphs in Figure 4 are shown in Table 14 below. By marginalizing in both graphs of Figure 4 over E and A, no additional edge is induced; see Wermuth (2011). The two concentration graphs in Figure 2 arise, the first four smoothed estimates of the odds-ratios in row 2 of Table 14 coincide with those estimated in Table 8 from the $LVCR$ table alone, and they are repeated in unchanged form for all level combinations of A, E.

For cases, Figure 4a) shows the selected concentration graph for which the overall fit of the model to is given by a chi-square value of 16.2 on 21 df. For the controls, Figure 4b) shows the selected regression graph which is Markov equivalent to a full-line concentration graph in the same nodes and in the same set of edges, since there is no collision V in the regression graph. The overall fit of the model in Figure 4b) is given by a chi-square value of 17.9 on 23 df; for general fitting procedures of regression graph models for categorical variables; see Marchetti and Lupparelli (2011).

The overall goodness-of-fit of these graphical log-linear models can typically be decomposed into a sequence of much smaller fitting steps. For instance for cases, the model $E \perp\!\!\!\perp VCRA$ splits into the sequence $E \perp\!\!\!\perp A|VCR$, $E \perp\!\!\!\perp V|CR$, $E \perp\!\!\!\perp V|R$, $E \perp\!\!\!\perp R$ with chi-square values of 5.3, 3.7, 2.9 1.2 on 8, 4, 2, 1 df, respectively, while for the additional fit of $A \perp\!\!\!\perp VR|C$ with 3.0 on 6 df, no single degree of freedom component can be significant.

Table 13 contains the estimates in two logit regressions. Choosing as highest order interactions terms the cliques in Figures 4a) or 4b) assures a good fit.

Table 13: Estimates for logit models of laryngeal cancer as response

response L	coeff	s_{coeff}	z_{obs}	coeff	s_{coeff}	z_{obs}
(const.)	−3.49	0.63	—	−3.37	0.42	—
V	1.33	0.72	—	1.32	0.71	—
C	0.64	0.57	—	0.29	0.50	—
R	0.30	0.64	—	0.34	0.32	—
VC	2.04	1.14	—	2.08	0.16	—
VR	1.31	0.84	—	1.30	0.83	—
CR	0.50	0.58	—	0.50	0.58	—
VCR	−3.34	1.32	−2.53	−3.39	1.32	−2.56
A	2.56	0.46	—	2.36	0.43	—
CA	−0.59	0.46	−1.26	—	—	—
E	1.95	0.64	—	1.96	0.38	—
AE	−1.88	0.50	−3.77	−1.87	0.49	−3.79
ER	0.04	0.65	0.06	—	—	—

Wilkinson's notation for the first logit models is $L:\ V*C*R+C*A+A*E+E*R$. This logit model is equivalent to the log-linear model which has as minimal sufficient tables, $LVRC, LCA, LAE, LAR$ and $VCRAE$, where the last table is the one of the regressor variables; see Haberman (1974). The fit is given by a chi-square value of 19.8 on 19 df.

The model can be simplified by excluding just two non-significant interaction terms CA and ER. This leads to model $L:\ V*C*R+A*E$ with a fit given by 21.4 on 21 df. The additivity of the effects of V, C, R and of A, E in this logit regression model explain why the odds-ratios for instance of L, V, estimated under model $L:\ V*C*R+A*E$, repeat in unchanged form for all level combinations of A, E.

Table 14: Odds-ratio estimates for L, V given $CRAE$ under two selected models, shown only for $E=0$; estimates are repeated in unchanged form for the eight levels of $E=1$

	level combinations of CRA given $E=0$							
$\hat{\mathcal{O}}\mathrm{dr}(LV\mid CRA)$ for:	000	100	010	110	001	101	011	111
logit model $L:\ A*E+V*C*R$	3.8	30.1	13.7	3.7	3.8	30.1	13.7	3.7
count estimates to Figures 4a), 4b)	4.7	15.1	12.1	5.4	4.7	15.1	12.1	5.4

As before in Table 8, the estimates based of the separate well-fitting concentration graphs for cases and controls are more smoothed than those of the minimally fitting logit regression. From both approaches, one concludes that each of five regressor variables is an important explanatory variable but that age at study time and level of education do not confound the dependence of L on V given C, R.

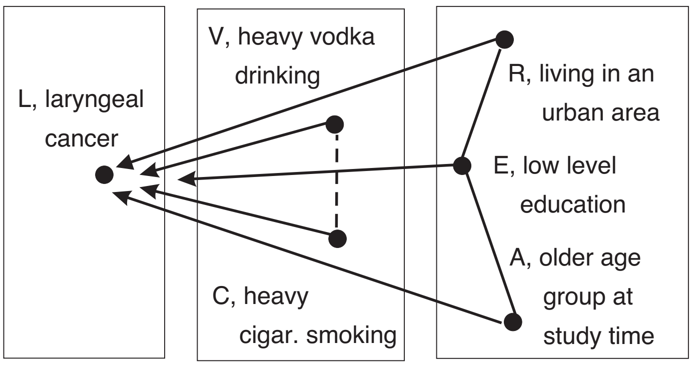

Figure 5: A regression graph summarizing important dependences; for L, it shows the relevant explanatory variables, but for V, C, R, A, E the independence structure among controls only.

For the general population, the fitted regression graph in Figure 5 and Figure 4b) imply in particular $V \perp\!\!\!\perp AE|CR$ since this follows from the complete independence $VC \perp\!\!\!\perp REA$. Thus by the collapsibility criterion of equation (5), the constant increase of the conditional relative risks of laryngeal cancer with heavy vodka drinking for both

groups of smokers in rural and urban communities do not change with the two age groups or with the two levels of formal education.

The differences in the cliques of the two concentration graphs for V, C, R, A, E to Figure 4 point instead to how cases differ mainly from controls with respect to the relations among these five features.

4 Understanding differences between cases and controls

Observed and estimated counts that exploits structure in the two separate samples of cases and controls are given for the $VRCAEL$ table in Table 19 of the Appendix. We use them now together with the cliques in the two graphs of Figure 4 to appreciate how the cases differ from the controls.

The two graphs in Figure 4 have three main distinguishing features. The subgraph induced by nodes VCR, is complete in Figure 4a) and a VC-edge isolated from node R in Figure 4b). The corresponding differences in exposure to heavy vodka drinking and cigarette smoking have already been described in the discussion of the observed VCR table in Section 3.1. Then, there is a V with inner node E connecting nodes A, R in Figure 4b) and no such path in 4a). Finally, there is an AC-edge in Figure 4a) and no such edge in 4b).

For controls, the graph in Figure 4b) implies $A \perp\!\!\!\perp R|E$, so that the almost equal observed $\text{odr}(EA|R=0) = 7.2$ and $\text{odr}(EA|R=1) = 7.5$ are, by equation (4), collapsible to a value near $\text{odr}(EA) = 7.1$. Similarly, the conditional odds-ratios for E, R given A reduce by equation (4) to $\text{odr}(ER) = 0.5$; see also Table 15.

Table 15: Lower level of education for controls by age and by living area

E, low	A, age group at study time		R, living area	
level educ.	33–50	51–65	urban	rural
0:= no	151	32	40	143
1:=yes	(34%) 77	(78%) 116	(62%) 68	(47%) 125
sum	228	148	108	268

For cases instead, the graph in Figure 3a) implies $E \perp\!\!\!\perp AR$. The observed percentages of cases with a low educational level are essentially the same level for both age groups in both living areas and estimated by the high overall rate of almost 80% (162 of 204). Thus, there is a kind of ceiling effect. Since almost all cases have the same low educational level, no effect of education can show up for the cases.

For both controls and for cases, a smaller percentage of the men in the older age group are heavy smokers; see Table 16. But the change from 25% to 21% for controls is not large enough to be statistically significant. For cases, the decrease is from 51% to 33%; significant at a 0.05 level with 5.5 on 1 df.

Table 16: Heavy cigarette smoking for cases and for controls by age

C, heavy	A, age group; controls		A, age group; cases	
cigar. smoking	33–50	51–65	33–50	51–65
0:= no	170	117	29	97
1:=yes	(25%) 58	(21%) 31	(51%) 30	(33%) 48
sum	228	148	59	145

As shown in Section 3, the risks for laryngeal cancer are highest for rural heavy smokers and for urban regular smokers; the features of these two groups are summarized next.

Table 17: Comparing features of cases with controls for urban, regular smokers

L, laryngeal	Observed percentages; counts			Means; (st.dev.)		
cancer	$V=1$	$A=1$	$E=1$	cV^*	cA^*	cC^*
controls; $n=207$	(4%) 9	(40%) 83	(48%) 99	1.1	46.8	17.2
				(5.3)	(10.1)	(3.2)
cases; $n=103$	(42%) 43	(79%) 81	(75%) 77	11.1	54.1	18.6
				(13.9)	(6.4)	(2.2)

where e.g. cA^* means that age is viewed as being continuous feature

In both Tables 17 and 18, one sees when changing from controls to cases, a tenfold increase in the rate of heavy vodka-drinking, a doubling of the risk of being in the older age group and a clear increase in the risk of having a lower level of education.

Table 18: Comparing features of cases with controls for rural, heavy smokers

L, laryngeal	Observed percentages; counts			Means; (st.dev.)		
cancer	$V=1$	$A=1$	$E=1$	cV	cA	cC
controls; $n=28$	(7%) 2	(36%) 10	(68%) 18	0.9	47.7	30.8
				(3.7)	(10.1)	(8.8)
cases; $n=25$	(68%) 17	(64%) 16	(84%) 21	14.7	51.7	29.1
				(11.4)	(6.7)	(7.8)

Even though the groups in Tables 17 and 18 differ by design in the amount of tobacco consumption, the relative risks of of laryngeal cancer due to heavy vodka drinking are similar when estimated as 15.1 and 12.1 using the separate count estimates for cases and controls; see Table 14. In particular cases and controls are, within both groups, quite comparable regarding the average number of cigarettes smoked per day. But within both living areas, the men who are cases are on average older than those who are controls, a much larger proportion of the cases has a low level of formal education compared to

the controls and heavy vodka consumption increases from an average of just one year of exposure to more than 10 years. Thus, these negative three features accumulate in a similar way in the two highest-risk groups of cases.

Nevertheless, it remains unexpected that no similar increase in risk is estimated for the urban communities as for the rural ones, when the tobacco consumption is increased to more than a pack of cigarettes per day.

5 Interpretation and discussion

5.1 General issues in the current case-control study

One main possibility to explain the differences in the two areas of living is that there may have been other risk factors at work in rural and in urban Polish communities at the time of study. These unmeasured competing risks may for instance be nutritional, environmental or occupational. If for instance, there was a higher average morbidity of men in urban communities, more of those who have been heavy smokers and vodka drinkers may have died from other causes before they could have participated in the study.

More specifically, the study group consists of men aged between 33 and 65 years in the second half of 1980, thus they all suffered as children or young adults from poor living conditions during and after the second world war. Since the nutritional status was at the time in most European countries on average much worse in urban than in rural communities, this may have led to a higher level of morbidity in urban than the rural participants.

In addition, in Polish cities the heating was frequently centralized, using coal-fired power stations nearby, while wood was preferably used for heating in rural areas. Thus exposure to coal dust or to the generally higher level of air pollution in the urban than in rural communities are plausible differences not reflected in the available data.

Drinking vodka of a particular poor quality or self-produced vodka, may be further risks that differ by regions. All these are hypotheses that need to be confirmed or rejected using more information on the participants of the present study or in similar studies of risks for laryngeal cancer.

Distortions may also have been introduced by the way in which the study participants were selected or in which they responded in the interviews. It has has been appreciated a long time ago, that whenever there is individual case-control matching on some variables, one gives up the chance of studying an interactive effect of the matching variables; see McKinlay (1977), but this argument does not apply to the sampling in the current study. Another source of possible distortions is a differential exposure-specific consent in controls and cases.

There was a high response rate for the controls while the case consent rate was lower.

In particular, because of the long-term exposure of the cases to the risk factors, some of the men may have been too ill to respond to the extended interview. This is a problem common to most case-control studies concerning a life-threatening illness.

However, an accumulation of several negative feature was seen in the current study for persons at highest risk. When similar analyses of further case-control data confirm these special combinations, it could help to set up feature-specific screening programs or help physicians to decide when to check for direct early symptoms in their own patients.

5.2 A summary of the proposed strategy of analysis.

The proposed new approach to analyzing case-control data aims at supplementing inference based modeling with evidence based arguments and to exploit the special features of case-control sampling for improved estimation of risks and for understanding major differences between cases and controls.

After the main research questions are set out, one defines categorical variables that lead to a cross-classification with at most a reasonable number of non-empty cells, to correlations that do not differ substantially from those of the raw data and to subgroups of cases and controls that are comparable with respect to important features known to relate to the disease under study.

The special sampling scheme of case-control studies always leads to samples from two different populations, one of the cases and one of the controls. After characterizing the independences and dependence structures supported by the separate samples for the regressor variables, the cliques of corresponding graphs lead directly to a well-fitting logit regression model. However, in such a logit regression, effects that are statistically significant only in the sample of the controls or of the cases but not in both, need not show as being important and hence could remain undetected.

Therefore, to identify important differences between cases and controls, the two separate well-fitting graphs, for the regressor variables alone, are combined with the relevant observed counts and basic data summaries. This leads to direct evidence which of the observed features of the diseased accumulate in a different way than in the general population from which the controls are sampled.

The goodness-of-fit tests used in the logit regression with the binary disease as response and for finding differential structure among the regressor variables alone depend on the saturated models obtained after the initial data processing steps. Thus, there is a remaining danger of relying too much on goodness of fit tests with these saturated models as reference. But, re-analyses of larger case-control studies are possible and feasible. They may help to confirm the more tentative results of a smaller study.

With more data than analyzed here, alternative data processing steps can also be contemplated which use more refined stratifications than binary variables can offer. The separate dependence structures of cases and controls together convincing data summaries

to supplement model based estimates, are the key for gaining more insights than with logistic regressions alone.

Appendix: Mixed count estimates for the two $VCRAE$ tables

From the observed counts for $VCRAEL$ and the estimated counts, obtained separately for cases and controls using the well-fitting models to Figures 4a) and 4b), the odds-ratios in Table 14 are obtained. For instance for the observation $21, 2, 4, 0$, in the first LV table at levels zero of each of the four remaining variables, the estimated counts, $23.79, 0.85, 1.40, 0.24$, lead to an estimated odds-ratio of 4.7.

Table 19: Observed and estimated* counts for the two $VCRAE$ tables

				$L = 0$, controls				$L = 1$, cases			
				$E = 0$		$E = 1$		$E = 0$		$E = 1$	
$VCRA$ levels				count	estim.*	count	estim.*	count	estim.*	count	estim.*
0	0	0	0	21	23.79	20	19.55	2	0.85	4	3.29
1	0	0	0	4	1.40	1	1.15	0	0.24	1	0.91
0	1	0	0	8	6.85	9	5.63	1	0.63	2	2.44
1	1	0	0	1	0.97	0	0.79	1	1.35	5	5.19
0	0	1	0	84	85.04	34	35.94	4	2.84	10	10.97
1	0	1	0	3	5.02	3	2.12	2	2.04	6	7.86
0	1	1	0	26	24.48	9	10.35	2	2.38	12	9.16
1	1	1	0	4	3.45	1	1.46	1	1.82	6	7.02
0	0	0	1	4	5.04	28	29.46	1	2.85	11	11.00
1	0	0	1	1	0.30	1	1.74	0	0.79	4	3.06
0	1	0	1	1	1.45	8	8.48	0	1.01	5	3.91
1	1	0	1	0	0.20	1	1.20	2	2.15	9	8.31
0	0	1	1	21	18.02	59	54.15	13	9.51	33	36.68
1	0	1	1	0	1.06	3	3.20	7	6.82	28	26.29
0	1	1	1	5	5.19	12	15.59	1	3.80	15	14.66
1	1	1	1	0	0.73	4	2.20	5	2.91	11	11.24

*estimates to concentration graphs; for controls in Figure 4b), for cases in Figure 4a)

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